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Model-Based Phase 3 Dose Selection for HIV-1 Attachment Inhibitor Prodrug BMS-663068 in HIV-1-Infected Patients: Population Pharmacokinetics/Pharmacodynamics of the Active Moiety, BMS-626529

Ishani Landry,[a*] Li Zhu,[a] Malaz Abu Tarif,[a] Matthew Hruska,[a] Brian M. Sadler,[b] Maria Pitsiu,[c] Samit Joshi,[d] George J. Hanna,[a] Max Lataillade,[d*] David W. Boulton,[a*] Richard J. Bertz[a]

Bristol-Myers Squibb, Research and Development, Princeton, New Jersey, USA[a]; ICON plc, Cary, North Carolina, USA[b]; ICON plc, Marlow, Buckinghamshire, United Kingdom[c]; Bristol-Myers Squibb, Research and Development, Wallingford, Connecticut, USA[d]

BMS-663068 is an oral prodrug of the HIV-1 attachment inhibitor BMS-626529, which prevents viral attachment to host CD4$^+$ T cells by binding to HIV-1 gp120. To guide dose selection for the phase 3 program, pharmacokinetic/pharmacodynamic modeling was performed using data from two phase 2 studies with HIV-1-infected subjects ($n = 244$). BMS-626529 population pharmacokinetics were described by a two-compartment model with first-order elimination from the central compartment, zero-order release of prodrug from the extended-release formulation into a hypothetical absorption compartment, and first-order absorption into the central compartment. The covariates of BMS-663068 formulation type, lean body mass, baseline CD8$^+$ T-cell percentage, and ritonavir coadministration were found to be significant contributors to intersubject variability. Exposure-response analyses showed a relationship between the $\log_e$-transformed concentration at the end of a dosing interval (C_{tau}) normalized for the protein binding-adjusted BMS-626529 half-maximal (50%) inhibitory concentration ($PBAIC_{50}$) and the change in the HIV-1 RNA level from the baseline level after 7 days of BMS-663068 monotherapy. The probability of achieving a decline in HIV-1 RNA level of >0.5 or >1.0 $\log_{10}$ copies/ml as a function of the $\log_e$-transformed $PBAIC_{50}$-adjusted C_{tau} after 7 days of monotherapy was 99 to 100% and 57 to 73%, respectively, for proposed BMS-663068 doses of 400 mg twice daily (BID), 600 mg BID (not studied in the phase 2b study), 800 mg BID, 600 mg once daily (QD), and 1,200 mg QD. On the basis of a slight advantage in efficacy of BID dosing over QD dosing, similar responses for the 600- and 800-mg BID doses, and prior clinical observations, BMS-663068 at 600 mg BID was predicted to have the optimal benefit-risk profile and selected for further clinical investigation. (The phase 2a proof-of-concept study AI438006 and the phase 2b study AI438011 are registered at ClinicalTrials.gov under numbers NCT01009814 and NCT01384734, respectively.)

As the management of HIV-1 infection requires lifelong treatment with sequential combination antiretroviral therapy (cART), antiretrovirals with a novel mechanism of action that can be used in combination with other agents to form active regimens following virologic failure are needed. This is particularly relevant for heavily treatment-experienced patients who, by definition, have limited remaining treatment options due to viral drug resistance, toxicity, and drug-drug interactions (1). For such patients, treatment guidelines recommend construction of a new regimen containing two or, ideally, three fully active agents where possible, on the basis of treatment history, viral drug resistance, and/or a new mechanism of action (1, 2).

BMS-663068 is an oral prodrug of the first-in-class HIV-1 attachment inhibitor BMS-626529, which prevents initial viral attachment to the host CD4$^+$ T cell by binding to the viral envelope protein gp120 (3). BMS-663068 is administered as an extended-release (ER) formulation, which is delivered to the gastrointestinal tract, where it is metabolized in the small intestine by alkaline phosphatase (ALP) to release the active moiety, BMS-626529 (4). BMS-626529 is then rapidly absorbed due to its efficient membrane permeability (4).

BMS-626529 is a human P-glycoprotein substrate and is primarily metabolized by esterases with contributions from a cytochrome P450 3A4 (CYP3A4) pathway (Bristol-Myers Squibb, data on file). Consistent with its CYP3A4 clearance, a clinical drug-drug interaction study showed that there was a moderate increase in BMS-626529 systemic exposure (a 53 to 68% increase in the maximum concentration [C_{max}] and a 45 to 54% increase in the area under the concentration-time curve for a dosing interval [AUC_{tau}]) when BMS-663068 was coadministered with the CYP3A4 inhibitor ritonavir (RTV) or ritonavir-boosted atazanavir (ATV/r) (5).

In a phase 2a study of BMS-663068 monotherapy with or without RTV boosting in treatment-naive and treatment-experienced subjects (AI438006 study; ClinicalTrials.gov registration num-

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Address correspondence to Richard J. Bertz, richard.bertz@bms.com.

* Present address: David W. Boulton, AstraZeneca LP, Gaithersburg, Maryland, USA. Ishani Landry, Eisai Inc., Woodcliff Lake, New Jersey, USA. Max Lataillade, Viiv Healthcare, Wallingford, Connecticut, USA.

ber NCT01009814), a maximum median decline in the plasma HIV-1 RNA level of 1.12 to 1.73 $\log_{10}$ copies/ml was observed after 8 days of treatment (6). The greatest virologic response (a change in the HIV-1 RNA level from the baseline level of $\geq$1 $\log_{10}$ copies/ml) to BMS-663068 treatment was in subjects with a baseline BMS-626529 half-maximal (50%) inhibitory concentration (IC_{50}) of $\leq$100 nM, with no change in efficacy detected across a wide range of doses. In a subsequent phase 2b dose-finding study (the AI438011 study; ClinicalTrials.gov registration number NCT01384734) with HIV-1-infected, treatment-experienced subjects who were screened for sensitivity to BMS-626529 (measured with the Monogram Biosciences PhenoSense Entry assay) prior to enrollment on the basis of the findings of the phase 2a study, 7 days of BMS-663068 monotherapy in a lead-in substudy resulted in a median decline in the HIV-1 RNA level of 0.69 $\log_{10}$ copies/ml with a dose of 400 mg twice daily (BID) and 1.28 to 1.44 $\log_{10}$ copies/ml with BMS-663068 doses of 600 mg once daily (QD), 800 mg BID, and 1,200 mg QD (7). BMS-663068 also had efficacy similar to that of the comparator treatment, ATV/r, following 24 weeks of cART with raltegravir (RAL) and tenofovir disoproxil fumarate (TDF) as backbone treatments in all arms: 69 to 80% of subjects across the BMS-663068 arms and 75% of subjects in the ATV/r arm achieved HIV-1 RNA levels of <50 copies/ml through week 24 (modified intent-to-treat population) (7). Furthermore, all doses were generally well tolerated, and there were no BMS-663068-related adverse events (AEs) leading to discontinuation (7).

The three primary aims of the analyses presented here were to develop a population pharmacokinetic (PK) model for BMS-626529 (determining significant covariates contributing to intersubject variability in BMS-626529 PKs); examine the PK/pharmacodynamic (PD) relationships between BMS-626529 systemic exposure and efficacy/safety variables; and use model-based trial simulations to facilitate optimal dose selection for the phase 3 study, in which BMS-663068 is being investigated in a heavily treatment-experienced population. The optimal dose was selected on the basis of the overall benefit-risk profile with the aim of maximizing the concentration at the end of a dosing interval (C_{tau}; 24 h for QD doses and 12 h for BID doses) while minimizing C_{max}, taking into consideration increases in BMS-626529 exposure in the presence of RTV (5) and a QTc effect seen at a supratherapeutic dose of 2,400 mg BID that did not occur at a therapeutic dose of 1,200 mg QD (8).

MATERIALS AND METHODS

Study data. Data from a phase 2a proof-of-concept study (the AI438006 study; NCT01009814) and a phase 2b study (the AI438011 study; NCT01384734), both with HIV-1-infected subjects, were included in the analysis (Tables 1 and 2). Two different formulations were tested: a wet granulation was developed (at 400-mg and 600-mg strengths) for the AI438011 study to overcome challenges in the process for the manufacture of the dry granulation formulation tested in the AI438006 study. Subjects in the AI438006 study received an ER dry-granulation formulation of BMS-663068 as monotherapy for 8 days, at doses of 600 mg with RTV boosting (RTV 100 mg) every 12 hours (Q12H), or 1,200 mg every bedtime, or 1,200 mg Q12H, with or without RTV boosting (100 mg RTV). Subjects in the AI438011 study received an ER wet granulation formulation of BMS-663068 at a dose of 400 mg BID, 600 mg QD, 800 mg BID, or 1,200 mg QD, all with a backbone of RAL at 400 mg BID and TDF at 300 mg QD, for up to 48 weeks (and the subjects were followed up to 96 weeks); a subset also participated in an elective 7-day monotherapy substudy prior to the main study. Only subjects with a baseline BMS-626529 half-maximal (50%) inhibitory concentration (IC_{50}) of <100 nM were included in the AI438011 study (7); the baseline BMS-626529 IC_{50} was not an exclusion criterion for the AI438006 study. Plasma samples were analyzed for BMS-626529 concentrations by a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay as previously described (6).

Objectives. The objectives of the population PK analysis were to develop a population PK model for BMS-626529 in HIV-1-infected subjects, quantify the potential influence of covariates that contribute significantly to intersubject differences in BMS-626529 PK parameters, and derive *post hoc* estimates of systemic exposure metrics (C_{max}, C_{tau}, and the average steady-state concentration [$C_{ss,avg}$]) for subsequent exposure-response analyses. The objective of the exposure-response analysis was to characterize the relationships between BMS-626529 systemic exposure and the antiviral response during both monotherapy and cART (at 24 weeks) and/or key safety parameters with or without normalization for viral susceptibility (the BMS-626529 IC_{50}). The objectives of the model-based dose simulation analysis were to predict the antiviral response as a function of BMS-626529 exposure for five potential BMS-663068 dosing regimens proposed for use in the phase 3 program (including a 600-mg BID dose, which has not yet been studied clinically) and to select an appropriate dose on the basis of the overall benefit-risk profile.

Population PK model for BMS-626529. The population PK model was developed using a nonlinear mixed-effect modeling approach, implemented in NONMEM (version 7.2.0) software, with a first-order conditional estimation model with interaction (FOCEI). A base model was developed using data from study AI438011 and applied to the combined data from studies AI438011 and AI438006, allowing for selected covariate effects (the effect of the formulation on relative bioavailability and input duration, the effect of RTV coadministration on relative bioavailability, and the effect of combination therapy and lean body mass [LBM] on clearance) to improve model stability. The full model approach was then implemented, in which all the remaining covariates were entered into the base model to investigate covariate parameter relationships with age, gender, race, treatment experience, laboratory parameters (creatinine clearance, liver enzyme levels, creatinine levels, total bilirubin levels), and baseline disease characteristics (plasma HIV-1 RNA levels, BMS-626529 IC_{50}, $CD4^+$ T-cell counts and percentages, and $CD8^+$ T-cell counts and percentages). This was followed by a stepwise backwards elimination at a significance level of a P value of <0.001, where the relative influence of each covariate was reevaluated by deleting it from the full model on an individual basis. Only statistically significant and/or clinically relevant relationships were included in the final model. The ability of the final population PK model to describe the observed data (central tendency and variability in exposures to BMS-626529) was evaluated using visual predictive checks.

Exposure-response analysis. Exploratory graphical exposure-response analyses were used to investigate potential relationships between BMS-626529 systemic exposure (C_{max}, C_{tau}, and $C_{ss,avg}$) and response and safety variables. Response variables included the antiviral response during BMS-663068 monotherapy (decline in the HIV-1 RNA level from the baseline, data from the AI438006 study and from subjects who participated in the monotherapy substudy in the AI438011 study) and during cART (the proportion of subjects with <50 HIV-1 RNA copies/ml through week 24 in the AI438011 study). Safety variables included selected AEs (on the basis of common treatment-related AEs in the AI438011 and AI438006 studies [headache, diarrhea, nausea, vomiting, and rash]) and changes in laboratory parameters (serum albumin, liver enzyme, creatine kinase, amylase, and total lipase levels and hematologic parameters [neutrophil, lymphocyte, monocyte, eosinophil, basophil, leukocyte, erythrocyte, and platelet counts and hemoglobin and hematocrit levels]).

On the basis of exploratory graphical exposure-response plots, linear and inhibitory maximum effect (E_{max}) models were used to quantify the

TABLE 1 Studies included in the analysis[a]

Study, study design	Study drug and dosage	No. of subjects	PK assessment	Response assessment
AI438006 (phase 2a proof-of-concept study with HIV-1-infected subjects), a randomized, open-label, multiple-dose, parallel study, monotherapy administered on days 1 to 8	Group 1, BMS-663068 at 600 mg Q12H + RTV at 100 mg Q12H; group 2, BMS-663068 at 1,200 mg QHS + RTV at 100 mg QHS; group 3, BMS-663068 at 1,200 mg Q12H + RTV at 100 mg Q12H; group 4, BMS-663068 at 1,200 mg Q12H + RTV at 100 mg QAM; group 5, BMS-663068 at 1,200 mg Q12H	50	Groups 1 and 3 to 5, intensive sampling after the a.m. dose on day 1 and after both doses on day 8 and sampling for determination of trough concn on days 5, 6, and 7; group 2, intensive sampling after p.m. dose on days 1 and 8 and sampling for determination of trough concn on days 5, 6, and 7	Change in plasma HIV-1 RNA level (log_{10} copies/ml) daily (day 1 to day 8); $CD4^+$ and $CD8^+$ T-cell count and percentage (day 1 and day 8); AEs; clinical laboratory values (days 1, 4, 8, and 11)
AI438011 (phase 2b study with HIV-1-infected subjects), a 7-day lead-in monotherapy substudy (with ~10 subjects from each BMS-663068 treatment group)	Group 1, BMS-663068 at 600 mg QD + RAL at 400 mg BID + TDF at 300 mg QD; group 2, BMS-663068 at 1,200 mg QD + RAL at 400 mg BID + TDF at 300 mg QD; group 3, BMS-663068 at 400 mg BID + RAL at 400 mg BID + TDF at 300 mg QD; group 4, BMS-663068 at 800 mg BID + RAL at 400 mg BID + TDF at 300 mg QD; group 5, ATV/r at 300/100 mg QD + RAL at 400 mg BID + TDF at 300 mg QD	32	Groups 1 to 4, intensive sampling after the a.m. dose on day 7 and sampling for determination of trough concn on days 2, 5, 6, and 7	Change in plasma HIV-1 RNA level (log_{10} copies/ml) (days 1, 2, 5, 6, and 7); $CD4^+$ and $CD8^+$ T-cell count and percentage (days 1 and 7); AEs, fasting chemistry and lipids (days 1 and 7); immunologic biomarkers (days 1 and 7)
AI438011 (phase 2b study with HIV-1-infected subjects), primary study with combination therapy for 96 wk	Group 1, BMS-663068 at 600 mg QD + RAL at 400 mg BID + TDF at 300 mg QD; group 2, BMS-663068 at 1,200 mg QD + RAL at 400 mg BID + TDF at 300 mg QD; group 3, BMS-663068 at 400 mg BID + RAL at 400 mg BID + TDF at 300 mg QD; group 4, BMS-663068 at 800 mg BID + RAL at 400 mg BID + TDF at 300 mg QD; group 5, ATV/r at 300/100 mg QD + RAL at 400 mg BID + TDF at 300 mg QD	196	Groups 1 to 4, intensive sampling in wk 2 (~10 subjects in each group) and sparse sampling of all subjects before the a.m. dose and 1–4 h after the a.m. dose at wk 4, 8, 12, 16, 20, and 24	Change in plasma HIV-1 RNA level (log_{10} copies/ml) (day 1; wk 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96; and/or ET); $CD4^+$ and $CD8^+$ T-cell count and percentage (day 1; wk 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96; and/or ET); AEs; fasting chemistry and lipids (day 1; wk 2, 4, 8, 12,16, 20, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96; and/or ET) immunologic biomarkers[b] (day 1; wk 2, 12, 24, 32, 48, and 96; and/or ET)

[a] All treatments were administered in the fed state. AE, adverse event; ATV/r, ritonavir-boosted atazanavir; BID, twice daily; ET, early termination; Q12H, every 12 h; QAM, every morning; QD, once daily; QHS, every night; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.
[b] The T-cell functional assay was performed only on weeks 24, 48, and 96 and/or at ET.

trends observed between BMS-626529 systemic exposure and the antiviral response (decline in the HIV-1 RNA level from the baseline) during BMS-663068 monotherapy with and without normalization for the protein binding-adjusted BMS-626529 IC_{50} ($PBAIC_{50}$) and with and without log_e transformation. $PBAIC_{50}$ was computed as $IC_{50} \times 473.48/0.12$, where 473.48 represents the molecular weight of BMS-626529, which was applied to convert the IC_{50} from molar to mass units, and 0.12 represents the free fraction in plasma, which was applied to account for protein binding. Log_{10}-transformed baseline HIV-1 RNA levels were tested as a covariate on the slope of the linear models and on the E_{max} in inhibitory E_{max} models. Logistic regression was used to evaluate possible relationships between BMS-626529 systemic exposure and response as part of cART (the proportion of subjects with HIV-1 RNA levels of <50 copies/ml through week 24).

Model-based simulations of BMS-663068 doses. The final population PK and exposure-response models were implemented using the Pharsight trial simulator (version 2.2.1; Pharsight, St. Louis, MO, USA) using Monte Carlo methods to simulate BMS-626529 PK profiles (C_{max}, $C_{ss,avg}$, and C_{tau}) and the resulting antiviral responses (the probability of achieving a decline in HIV-1 RNA levels of >0.5 or >1.0 log_{10} copies/ml from the baseline level as a function of BMS-626529 exposure, with a decline of >0.5 log_{10} copies/ml being based on FDA draft guidance for clinical trial endpoints in heavily treatment-experienced patients) (9) following 7 days of BMS-663068 monotherapy for proposed BMS-663068 doses of 400, 600, and 800 mg BID and 600 and 1,200 mg QD. Only subjects with a baseline BMS-626529 IC_{50} of <100 nM were included in the phase 2b study (AI438011), but this cutoff point was not applied to the phase 2a study (AI438006) or to the simulation. Therefore, IC_{50}s were redetermined at random from all baseline values observed in studies AI438006 and AI438011 up to a maximum of 10 μM. The distributions of PK parameters were described by the vector of fixed effects and the diagonal Ω matrix.

Simulations were performed for 10,000 hypothetical subjects (2,000 subjects for each of the five proposed dosing regimens).

RESULTS

Population PK analysis. A total of 4,377 plasma BMS-626529 concentrations from 244 subjects (50 from the AI438006 study and 194 from the AI438011 study) were included in the population PK analysis. The PKs of BMS-626529 were adequately described by a two-compartment model with first-order elimination from the central compartment and the zero-order release of the

TABLE 2 Baseline demographics and disease characteristics[a]

Characteristic	Value[b]
Median (range) baseline value for:	
Age, yrs	40.0 (20.0–70.0)
Wt, kg	71.0 (40.0–151.3)
LBM, kg	54.0 (32.0–76.0)
No. (%) of subjects by gender	
Male	166 (68)
Female	78 (32)
No. (%) of subjects by race	
White	122 (50)
Black/African-American	59 (24)
Asian	2 (1)
Other[c]	61 (25)
No. (%) of subjects by BMS-663068 formulation	
Dry granulation	50 (20)
Wet granulation	194 (80)
No. (%) of subjects concomitantly receiving RTV (study AI438006 only)	40 (16)
No. (%) of subjects with prior therapy experience	
Experienced	210 (86)
Naive (study AI438006 only)	34 (14)
Median (range) baseline value for:	
HIV-1 RNA level, $\log_{10}$ no. of copies/ml	4.8 (1.7–6.8)
$CD4^+$ T-cell count, no. of cells/mm^3	271 (32–921)
$CD8^+$ T-cell count, no. of cells/mm^3	886 (180–3162)
$CD8^+$ T-cell count, %	18 (3–40)
$CD4^+$ T-cell count, %	57 (32–83)

[a] LBM, lean body mass; RTV, ritonavir.
[b] Data are for 244 subjects for all characteristics except for $CD4^+$ and $CD8^+$ T-cell counts, for which the data are for 240 subjects.
[c] The majority of the subjects within the other category reported themselves to be multiracial.

BMS-663068 prodrug from the ER formulation into a hypothetical absorption depot compartment, followed by first-order absorption into the central compartment (Fig. 1). A factor of 0.81, based on the relative molecular weights of BMS-663068 and BMS-626529, was included as a bioavailability fraction for the central

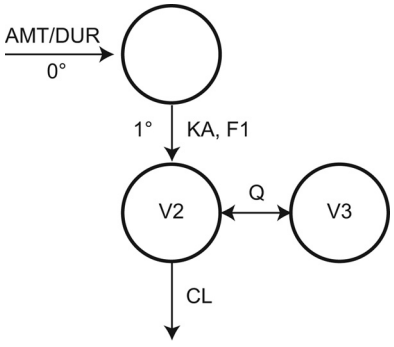

FIG 1 BMS-626529 population PK model. AMT, administered treatment; CL, apparent oral clearance; DUR, estimated duration of BMS-663068 release from the extended-release formulation; F1, relative bioavailability; KA, first-order absorption rate constant; Q, intercompartmental clearance; V2, volume of distribution of the central compartment; V3, volume of distribution of the peripheral compartment.

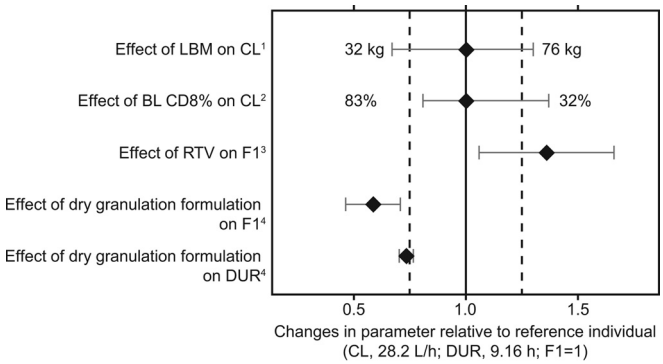

FIG 2 Predicted fold change in PK parameters due to covariate effects. Categorical covariates were RTV coadministration and dry granulation formulation, where the diamonds represent the estimated change in the parameter due to the covariate and whiskers represent the 95% confidence interval of the estimate. Continuous covariates were LBM and the baseline $CD8^+$ percentage, where the diamonds represent the reference values and whiskers represent the change in the parameter at the minimum and maximum value of the covariate (noted on plot). Dashed lines represent a 25% change in the parameter relative to the value for the reference individual who received the wet granulation formulation without RTV. 1, exponent for the effect of the median-normalized baseline LBM on CL; 2, exponent for the effect of the median-normalized baseline $CD8^+$ percentage on CL; 3, change relative to the reference treatment (BMS-663068 dosed without RTV); 4, change relative to the reference formulation (the wet granulation). BL, baseline; CL, apparent oral clearance; DUR, estimated duration of BMS-663068 release from the extended-release formulation; F1, relative bioavailability; LBM, lean body mass; RTV, ritonavir.

compartment to convert the dose of the BMS-663068 prodrug to the BMS-626529 equivalent dose. Following the backward elimination of the covariate parameter relationships from the full covariate model, the BMS-663068 formulation type (wet or dry granulation) was found to have a statistically significant effect ($P < 0.001$) on the duration of BMS-663068 release (DUR) from the ER formulation and on relative bioavailability. DUR was 26% lower and relative bioavailability was 41% lower for the dry granulation formulation than for the wet granulation formulation. In addition, the continuous covariates LBM and the baseline percentage of $CD8^+$ T cells were found to have a statistically significant ($P < 0.001$) effect on apparent oral clearance (CL) (Fig. 2), with CL increasing 0.770 liter/h for every unit increase in LBM above the reference value of 54 kg and CL decreasing 0.548 liter/h for every unit increase in the baseline percentage of $CD8^+$ T cells above the reference value of 57%. These covariate parameter relationships were included in the final model. Although the effect of RTV coadministration on relative bioavailability was statistically significant only at the level of a P value of <0.05 ($P = 0.0035$), it was also included in the final model due to clinical interest and the magnitude of the effect (a 36% increase in relative bioavailability) (Fig. 2). Parameter estimates for the final population PK model are shown in Table 3. Prediction-corrected visual predictive checks confirmed that the final model adequately described the observed BMS-626529 steady-state concentrations in HIV-1-infected subjects (Fig. 3).

Exposure-response analyses. The monotherapy and combination therapy exposure-response analyses performed at the subject level included data from 77 subjects who received BMS-663068 monotherapy (48 from the AI438006 study and 29 from the AI438011 study) and 190 subjects who received BMS-663068 as part of cART (the AI438011 study). Data for two subjects from

TABLE 3 Estimated population PK parameters for the final model[a]

Effect and parameter	Units	Estimate (% CV)	% RSE	95% CI	
				Lower	Upper
Fixed effects					
CL (θ1)	Liters per hour	28.2	3.39	26.3	30.1
V_2 (θ2)	Liters	32.3	16.2	22.1	42.5
KA (θ3)	Liters per hour	1.22	9.92	0.983	1.46
Q (θ4)	Liters per hour	14.5	5.17	13.0	16.0
V_3 (θ5)	Liters	85.5	6.32	74.9	96.1
DUR (θ6)	Hours	9.16	1.06	8.97	9.35
Effect of dry formulation on F_1 (θ7)[b]		0.586	10.6	0.464	0.708
Effect of dry formulation on DUR (θ8)[b]		0.736	2.11	0.706	0.766
Effect of RTV on F_1 (θ9)[c]		1.36	11.1	1.06	1.66
Effect of baseline LBM on CL (θ10)[d]		0.770	18.8	0.486	1.05
Effect of baseline CD8% on CL (θ11)[e]		−0.548	28.6	−0.856	−0.240
Interindividual random effects					
CL, variance		0.132 (36.3)	10.8	0.104	0.160
V_2, variance		1.12 (106.0)	18.7	0.710	1.53
V_3, variance		0.295 (54.3)	18.6	0.187	0.403
Residual error random effects, proportional error		0.341 (58.4)	2.12	0.327	0.355

[a] CI, 95% confidence interval; CL, apparent oral clearance; CV, coefficient of variation; DUR, estimated duration of BMS-663068 release from the extended-release formulation; F_1, relative bioavailability; KA, first-order absorption rate constant; LBM, lean body mass; Q, intercompartmental clearance; RSE; relative standard error of the estimate; RTV, ritonavir; V_2, volume of distribution of the central compartment; V_3, volume of distribution of the peripheral compartment. $CL = \theta1 \times (LBM/54)^{\theta10} \times (BL\ percentage\ of\ CD8\ cells/57)^{\theta11}$; $F_1 = 0.81 \times \theta7^{FORM}$ (where FORM represents the formulation; if a dry granulation is used, FORM is equal to 1; otherwise, FORM is equal to 0) $\times\ \theta9^{RTV}$ (where RTV represents RTV coadministration; if RTV is coadministered, RTV is equal to 1; otherwise, RTV is equal to 0); 0.81 converts the dose of BMS-663068 to the BMS-626529 dose equivalent; $DUR = \theta6 \times \theta8^{FORM}$ (if a dry granulation is used, FORM is equal to 1; otherwise, FORM is equal to 0).

[b] Change relative to the value obtained with the reference formulation (wet granulation).

[c] Change relative to the value obtained with the reference treatment (BMS-663068 dosed without RTV).

[d] Exponent for the effect of the median-normalized baseline LBM on CL.

[e] Exponent for the effect of the median-normalized baseline percentage of $CD8^+$ cells on CL.

the AI438006 study were excluded from the exposure-response analyses due to missing baseline BMS-626529 IC_{50}s, and data for four subjects from the AI438011 study were excluded due to missing viral load data at baseline.

During BMS-663068 monotherapy, baseline viral drug susceptibility ($PBAIC_{50}$) was the most influential factor determining the magnitude of the decline in HIV-1 RNA levels. PK/PD analysis was conducted on the day after 7 days of monotherapy. The most compelling relationships observed were those between $\log_e$-transformed $PBAIC_{50}$-adjusted $C_{ss,avg}$ or C_{tau} and the change in HIV-1 RNA levels from the baseline ($\log_{10}$ number of copies/ml). There were no discernible differences between C_{tau} and $C_{ss,avg}$ when they were used in conjunction with $PBAIC_{50}$ to predict the decline in HIV-1 RNA levels during monotherapy. The lack of a difference could be attributed to the normalization for $PBAIC_{50}$, which resulted in a minimal difference in the drop in the viral load predicted. Hence, C_{tau} was selected for use in the analysis, as it is generally considered a more reliable predictor of antiviral activity (Fig. 4) (1). No trends were observed for any other efficacy or safety variables during monotherapy.

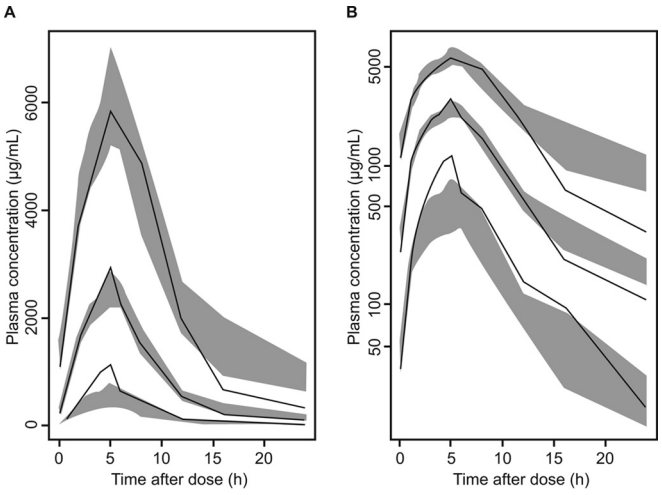

FIG 3 Prediction-corrected visual predictive checks for the final population PK model. (A) Linear plot; (B) semilogarithmic plot. Solid black lines, 5th, 50th, and 95th percentiles of the prediction-corrected observations from bottom to top, respectively; gray bands, 90% confidence intervals for the 5th, 50th, and 95th percentiles of the prediction-corrected simulated values (500 replicates) from bottom to top, respectively.

During cART, C_{tau} was not a significant predictor of the antiviral response (the proportion of subjects with HIV-1 RNA levels of <50 copies/ml through week 24), regardless of normalization for $PBAIC_{50}$ or $\log_e$ transformation. To determine whether there was an exposure effect, the predicted influence of $\log_e(C_{tau})$ was investigated in the models with the lowest probability for an exposure effect during cART (i.e., $\log_e[C_{tau}]$ at week 24 in the observed population). The results are shown in Fig. 5. No exposure-response trends were observed for any of the safety variables (with or without normalization for the BMS-626529 IC_{50}) during 24 weeks of cART with RAL and TDF.

Model-based simulations to identify a BMS-663068 dose for use in phase 3 studies. As no exposure-response trends were

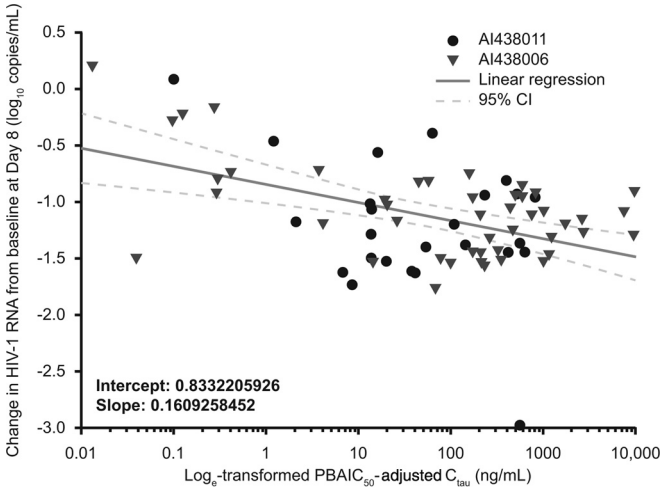

FIG 4 Relationship between $PBAIC_{50}$-adjusted C_{tau} and change in the HIV-1 RNA level from the baseline level (log_{10} copies/ml) after 7 days of BMS-663068 monotherapy. CI, confidence interval; C_{tau}, concentration at the end of a dosing interval; $PBAIC_{50}$, protein binding-adjusted BMS-663068 half-maximal (50%) inhibitory concentration.

observed following 24 weeks of combination therapy in the AI438011 study, the responses observed following 7 days of BMS-663068 monotherapy were used to discriminate between BMS-663068 doses. The most appropriate time point selected for analysis was after 7 days of dosing, as it was the latest time point at which observations were available from both the AI438006 and AI438011 studies during monotherapy. PKs/PDs were assessed on day 8. Simulations were used to assess the probability of achieving a decline in HIV-1 RNA levels of >0.5 or >1 log_{10} copies/ml after 7 days of BMS-663068 monotherapy as a function of the BMS-626529 log_e-transformed $PBAIC_{50}$-adjusted C_{tau} for the five proposed BMS-663068 dosing regimens (Fig. 6). The baseline HIV-1 RNA level was included as a significant covariate in the response. Simulations incorporated intersubject variability and sampled the distributions of the covariates $CD8^+$ T-cell percentage, LBM, the

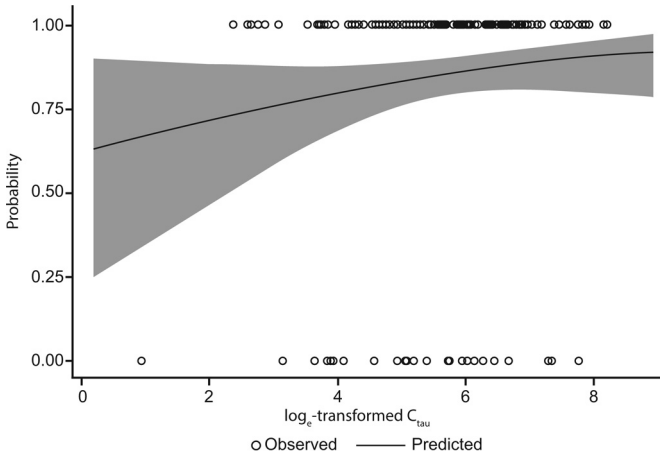

FIG 5 Model-predicted relationship between an HIV-1 RNA level of <50 copies/ml and $\ln(C_{tau})$ at week 24 (observed population). The predicted probabilities of a value of 1 for the antiviral response variable for the observed population at a baseline log_{10} HIV-1 RNA level of 4.795 log_{10} copies/ml are shown. C_{tau}, concentration at the end of a dosing interval.

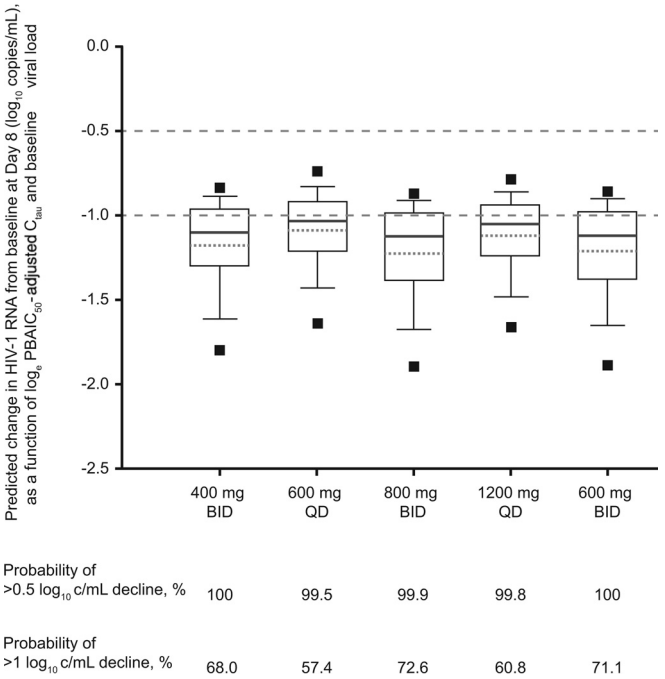

FIG 6 Probability of achieving a decline in the HIV-1 RNA level of >0.5 log_{10} copies/ml and >1 log_{10} copies/ml from the baseline level as a function of the BMS-626529 log_e $PBAIC_{50}$-adjusted C_{tau}. Closed squares at bottom and top for each dose, 5th and 95th percentiles, respectively; bottoms and tops of bars, 10th and 90th percentiles, respectively; bottoms and tops of large open squares, interquartile range; solid horizontal bars, medians; dotted lines, means; dashed lines, target change in viral loads. BID, twice daily; C_{tau}, concentration at the end of a dosing interval; $PBAIC_{50}$, protein binding-adjusted BMS-663068 half-maximal (50%) inhibitory concentration; QD, once daily; log_{10} c/ml, log_{10} copies/ml.

baseline HIV-1 RNA level (log_{10} copies/ml), and the expected range in baseline BMS-626529 $PBAIC_{50}$ values (on the basis of values observed in studies AI438006 and AI438011). The probability of achieving a decline in HIV-1 RNA levels of >0.5 log_{10} copies/ml was 99 to 100% for all dosing regimens. The probability (for each regimen) of achieving a decline in HIV-1 RNA levels of >1 log_{10} copies/ml was 68% for the dose of 400 mg BID, 57% for the dose of 600 mg QD, 71% for the dose of 600 mg BID, 73% for the dose of 800 mg BID, and 61% for the dose of 1,200 mg QD. When the data for subjects with a baseline BMS-626529 IC_{50} of >100 nM were excluded, no notable difference between the dosing regimens was observed for a target decline in the HIV-1 RNA level of >0.5 log_{10} copies/ml.

DISCUSSION

Optimal dose selection requires the evaluation of inter- and intrasubject variability in the PKs and PDs of a drug. This analysis used data from two phase 2 studies (AI438006 and AI438011) to create a nonlinear mixed-effects model to describe the PKs of BMS-626529 and an exposure-response model to predict antiviral activity following repeat oral administration of BMS-663068 in HIV-1-infected subjects. The results, in combination with clinical observations and analysis of the overall benefit-risk profile, were then used to help select an optimal dose for the phase 3 program.

The PKs of BMS-626529 were adequately described by a two-compartment model incorporating a zero-order input into a hy-

pothetical depot compartment to account for the release of the BMS-663068 prodrug from the ER formulation and a first-order input from the depot compartment to the plasma compartment to account for both the metabolism of BMS-663068 to BMS-626529 by ALP and the absorption of BMS-626529 into plasma. The apparent oral clearance of BMS-626529 increased as lean body mass increased and baseline $CD8^+$ counts decreased. The clinical significance of these effects is not known. In addition, the estimated duration of prodrug release from the ER formulation was shorter, and relative bioavailability was lower for the dry granulation formulation of BMS-663068 (used in the AI438006 study) than the wet granulation formulation (used in the AI438011 study). The wet formulation will be used in the phase 3 program. Although the effect of RTV coadministration was not statistically significant, RTV was included in the model for clinical interest due to a predicted 36% increase in BMS-626529 exposure on coadministration with RTV.

Exposure-response relationships were explored for various key efficacy and safety endpoints both during BMS-663068 monotherapy and during combination therapy with RAL and TDF, but a relationship was established only between BMS-626529 exposure and the antiviral response during BMS-663068 monotherapy at doses of 400 mg BID, 600 mg QD, 800 mg BID, and 1,200 mg QD. Baseline viral drug susceptibility appeared to be the most influential factor in determining the magnitude of the decline in HIV-1 RNA levels during BMS-663068 monotherapy, in line with observations from the AI438006 study (6, 10), and the most compelling exposure-response relationships were observed with $\log_e$-transformed $PBAIC_{50}$-adjusted $C_{ss,avg}$ and C_{tau}. There were no significant differences between the $C_{ss,avg}$ and C_{tau} models, so, as C_{tau} is generally considered to be a better predictor of antiviral activity, the C_{tau} model was selected for the modeling and simulation analysis.

The probability of achieving a decline in the HIV-1 RNA level of >0.5 $\log_{10}$ copies/ml from the baseline at an early time point is recommended as a primary endpoint for trials of antiretroviral agents with heavily treatment-experienced patients (9). The simulation analysis showed that all proposed phase 3 study BMS-663068 doses (400 mg BID, 600 mg BID, 800 mg BID, 600 mg QD, 1,200 mg QD) had a similar probability of achieving a decline in the HIV-1 RNA level of >0.5 $\log_{10}$ copies/ml after 7 days of BMS-663068 monotherapy. However, the BID doses had a slightly higher probability of achieving a decline in the HIV-1 RNA level of >1 $\log_{10}$ copies/ml after 7 days of BMS-663068 monotherapy than the QD doses. While the dosing regimen with BMS-663068 at 600 mg BID was not studied in the phase 2b study, it was selected for study in the phase 3 clinical program investigating BMS-663068 for use in heavily treatment-experienced individuals. This decision was based on the findings of the current analysis, as detailed below.

First, based on the simulations, BID dosing of BMS-663068 was associated with a slightly higher probability of achieving a target decline in the HIV-1 RNA level of >1 $\log_{10}$ copies/ml than QD dosing, and the 600-mg BID and 800-mg BID doses had similar probabilities of achieving a target decline of >1 $\log_{10}$ copies/ml. Second, on the basis of clinical data from the AI438011 study (7), the 400-mg BID dose led to a decline in the HIV-1 RNA level of <1 $\log_{10}$ copies/ml, whereas a total daily dose of BMS-663068 at 1,200 mg (1,200 mg QD) had an efficacy and safety profile similar to that of a total daily dose of 1,600 mg (800 mg BID) when administered as cART for 24 weeks.

The 600-mg BID dose is expected to result in a C_{max} lower than that achieved with both the 800-mg BID and 1,200-mg QD doses when they are coadministered with a boosted protease inhibitor (PI), which would allow a greater therapeutic margin from the supratherapeutic dose of 2,400 mg BID that is associated with C_{max}-driven QTc interval prolongation (8). This consideration may be important, because BMS-663068 could be used in combination with antiretroviral agents, such as RTV-boosted PIs, that have been shown to increase the BMS-626529 C_{max} by ~50 to 68% (5, 11). This observation may be particularly relevant for heavily treatment-experienced individuals, such as those in the phase 3 study population, who are likely to be receiving RTV-boosted PIs. Notably, the increases in BMS-626529 exposure achieved when BMS-663068 was coadministered with RTV-boosted PIs in previous studies did not affect the safety profile of BMS-663068 and are therefore not expected to be clinically relevant (5, 11). Importantly, despite the predicted increase in the BMS-626529 C_{max} achieved following the administration of BMS-663068 at 800 mg BID and 1,200 mg QD compared with that achieved following the administration of BMS-663068 at 600 mg BID, neither dose has been associated with any incidence of QTc prolongation (8). Although BMS-663068 at 800 mg BID was efficacious and well tolerated in the phase 2b study, only one regimen will be investigated in the phase 3 program. To minimize exposure, the 600-mg BID dose was selected because of its predicted lower C_{max}.

The limitations of this investigation include the relatively small subject number and a baseline BMS-626529 IC_{50} cutoff that was applied in only one of the two studies used in the analysis. The antiviral response was predicted to be moderately better in subjects with more susceptible virus at baseline. However, when subjects with a baseline BMS-626529 IC_{50} of >100 nM were excluded from the analysis. there was no notable difference in the probability of achieving a target HIV-1 RNA level decline of >0.5 $\log_{10}$ copies/ml and only a $\leq 6\%$ increase in the probability of achieving a target HIV-1 RNA level decline of >1 $\log_{10}$ copies/ml. Sensitivity testing will be performed at screening in the phase 3 program and the data will be analyzed retrospectively, but sensitivity will not be an exclusion criterion. It should also be noted that the lack of difference in $PBAIC_{50}$-adjusted C_{tau} and $C_{ss,avg}$ resulted in a minimal difference in predicting the viral load drop; hence, C_{tau} was selected as the important exposure measure for the modeling simulation. As BID dosing is associated with a higher C_{tau}, the model predicts that a dose of 600 mg BID produces slightly better viral suppression than one of 1,200 mg QD, although this cannot be definitively assessed from the available data set.

In conclusion, simulations showed that BID dosing of BMS-663068 had an advantage over QD dosing and that there was a similar probability of achieving a decline in the HIV-1 RNA level of >1 $\log_{10}$ copies/ml using BMS-663068 doses of 600 mg BID and 800 mg BID. Combined with clinical and safety observations, the BMS-663068 dose of 600 mg BID will be investigated in a phase 3 trial with heavily treatment-experienced subjects.

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We declare the following conflicts of interest: Brian M. Sadler reports other interests (he holds GlaxoSmithKline stock) outside the submitted work. David W. Boulton was a Bristol-Myers Squibb employee and shareholder at the time that the work was performed; he is a current AstraZeneca employee and shareholder. Ishani Landry was a Bristol-Myers Squibb employee and shareholder at the time that the work was performed; she is a current Eisai employee and shareholder. Max Lataillade was a Bristol-Myers Squibb employee and shareholder at the time that the work was performed; he is a current Viiv Healthcare employee and shareholder. Malaz Abu Tarif, Richard J. Bertz, George J. Hanna, Matthew Hruska, Samit Joshi, and Li Zhu are all Bristol-Myers Squibb employees and shareholders. Maria Pitsiu has no conflicts to disclose.

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REFERENCES

1. **U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.** 2015. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. U.S. Department of Health and Human Services, Washington, DC. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 2015.
2. **European AIDS Clinical Society.** 2014. European AIDS Clinical Society guidelines, version 7.1. European AIDS Clinical Society, Brussels, Belgium. http://www.eacsociety.org/files/guidelines_english_71_141204.pdf. Accessed March 2014.
3. **Langley DR, Kimura SR, Sivaprakasam P, Zhou N, Dicker I, McAuliffe B, Wang T, Kadow JF, Meanwell NA, Krystal M.** 2015. Homology models of the attachment inhibitor BMS-626529 bound to gp120 suggest a unique mechanism of action. Proteins **83:**331–350. http://dx.doi.org/10.1002/prot.24726.
4. **Brown J, Chien C, Timmins P, Dennis A, Doll W, Sandefer E, Page R, Nettles RE, Zhu L, Grasela D.** 2013. Compartmental absorption modeling and site of absorption studies to determine feasibility of an extended-release formulation of an HIV-1 attachment inhibitor phosphate ester prodrug. J Pharm Sci **102:**1742–1751. http://dx.doi.org/10.1002/jps.23476.
5. **Zhu L, Hruska M, Hwang C, Shah V, Furlong M, Hanna GJ, Bertz R, Landry IS.** 2015. Pharmacokinetic interactions between BMS-626529, the active moiety of the HIV-1 attachment inhibitor prodrug BMS-663068, and ritonavir or ritonavir-boosted atazanavir in healthy subjects. Antimicrob Agents Chemother **59:**3816–3822. http://dx.doi.org/10.1128/AAC.04914-14.
6. **Nettles R, Schurmann D, Zhu L, Stonier M, Huang SP, Chang I, Chien C, Krystal M, Wind-Rotolo M, Ray N, Hanna GJ, Bertz R, Grasela D.** 2012. Pharmacodynamics, safety, and pharmacokinetics of BMS-663068, an oral HIV-1 attachment inhibitor in HIV-1-infected subjects. J Infect Dis **206:**1002–1011. http://dx.doi.org/10.1093/infdis/jis432.
7. **Lalezari JP, Latiff GH, Brinson C, Echevarría J, Treviño-Pérez S, Bogner JR, Thompson M, Fourie J, Sussmann Pena OA, Mendo Urbina FC, Martins M, Diaconescu IG, Stock DA, Joshi SR, Hanna GJ, Lataillade M, AI438011 Study Team.** 2015. Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial. Lancet HIV **2:**e427–e437. http://dx.doi.org/10.1016/S2352-3018(15)00177-0.
8. **Hruska MW, Savant IA, Anderson JA, Shah V, Chang I, Adamczyk R, Furlong M, Hanna GJ, Bertz R, Zhu L.** 2014. Thorough QT/QTc trial to evaluate the effect of the HIV-1 attachment inhibitor BMS-626529, administered as its prodrug, BMS-663068, on QTc intervals, poster P_54. Abstr 15th Int Workshop Clin Pharmacol HIV Hepatitis Ther, Washington, DC.
9. **Food and Drug Administration.** June 2013. Food and Drug Administration guidance for industry. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Food and Drug Administration, Silver Spring, MD. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf. Accessed June 2015.
10. **Ray N, Hwang C, Healy MD, Whitcomb J, Lataillade M, Wind-Rotolo M, Krystal M, Hanna GJ.** 2013. Prediction of virological response and assessment of resistance emergence to the HIV-1 attachment inhibitor BMS-626529 during 8-day monotherapy with its prodrug BMS-663068. J Acquir Immune Defic Syndr **64:**7–15. http://dx.doi.org/10.1097/QAI.0b013e31829726f3.
11. **Savant Landry I, Tao X, Anderson J, Hesney M, Stonier M, Lubin S, Wang J, Hanna GJ, Boulton DW.** 2015. HIV-1 attachment inhibitor prodrug BMS-663068: interactions with DRV/r and/or ETR, poster 523. Abstr Conf Retroviruses Opportunistic Infect, Seattle, WA.